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(54) A formulation for iron chelation and a process for preparing same

(57) A pharmaceutical formulation useful for treating patients suffering from thalassemia, which comprises powder of Anemonin Pretensis in an amount in the range of 0.02 to 0.12 wt % of the formulation, quinine sulphate in an amount in the range of 0.0005 to 0.003 wt % of the formulation, distilled or demineralised water in an amount in the range of 0 to 40 wt % of the formulation and, edible solvent 99.88 to 60 wt % of the formulation; and a process for preparing the formulation by mixing the above ingredients.

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Description

This invention relates to a formulation for iron-chelation. The formulation of the present invention is useful for treating patients suffering from the disease of Thalassemia.

This invention relates particularly to a formulation useful for the treatment of patients suffering from the disease of Thalassemia with increased therapeutic efficacy.

Thalassemia is a dreaded disease among children because of genetic disorder. The disease is caused due to hereditary disorders connected with defective haemoglobin synthesis, characterised by hypochromia, microcytosis, haemolysis and a variable degree of anaemia. Thalassemia involves a heterogeneous group of molecular defects and present with a wide spectrum of clinical expressions.

Patients suffering from Thalassemia suffer from anaemias with decreased or absence of synthesis of a globin chain of a normal haemoglobin. The patients of thalassemia are broadly classified into two major groups according to the affected globin chain.

The patients suffering from Alpha (α) Thalassemia are associated with decreased or absence of α - chain synthesis. The patients suffering from Beta (β) Thalassemia are associated with decreased or absence of β - chain synthesis.

Rarely one may find also patients suffering from Thalassemia delta (δ) and Gamma (γ) chain disorders, as well as those associated abnormal hemoglobin structure (e.g. Hb Lepose and Hb Constant Spring). Such types of disease which also contribute to the Thalassemia Syndromes.

The disease Thalassemia occurs world wide with a particular high incidence in the Mediterranean basin and in the South-East Asia. Malaria is also endemic in these areas - a significant fact since indirect evidence suggests that - Thalassemia (major) heterozygosity confers protection against malaria.

The β - Thalassemia or Thalassemia major type of the disease comprises a heterogeneous group of disorder usually characterised by absence of (β) or decreased (β) globin synthesis.

The type of - Thalassemia is also classified according to the severity of the anaemia. These clinical classification serves to differentiate homozygous (Thalassemia intermedia or Thalassemia major) from heterozygous state (Thalassemia minima or Thalassemia minor). Though, it does not reflect genetic mutation, Thalassemia (minor) is a reduced rate of β - globin synthesis, with an increased α - β globin chains, but it not threat to a normal life.

In case of Thalassemia (Major) also known as Cooley's anaemia, Mediterranean anaemia and Von - Jacksch's anaemia is characterised by marked anaemia (ranging from 1 to 6 gm/dl of homoglobin), severe hemolysis and ineffective erythropoiesis. The diagnosis is made in the 1st year of the life of the patient, often as early as 3 months old baby. In the case of Thalassemia (Major), iron in the haemoglobin also breaks down and gets deposited in the vital organs of the body of the patients e.g. liver, kidney, spleen, heart etc. This is also known as iron overloading in the body and the life span of the child suffering from Thalassemia (major) becomes unpredictable. Every year out of 1,00,000 children born with Thalassemia (major) in the world, 10,000 are born in India.

The method which is available hitherto for the treatment of Thalassemia (major) is by the life long blood transfusion coupled with the taking of the drug called 'Desferal' daily intermuscular. The chemical name of the drug is Deferoxamine Methane Sulphonate and the chemical formula is $C_{28}H_{52}N_4O_{11}S$.

Presently followed therapy is giving injection of Desferal for the excretion of iron from the body of the patient through urinary excretion. It was found by medical profession that Desferal had many side effects like swelling of limbs, stiffness in joints and may inhibit a number of tumour cell proliferation, parasite growth and the proliferation of the cerebral Malaria Parasite, Plasmodium Faliparum.

In addition, the above drug is to be injected daily under the skin of the patient in a controlled manner in such a way to avoid any side reaction causing allergic conditions. Such a treatment is a highly painful. The treatment is also costly as the vial containing 500 mg of dry active substance will cost about US \$ 10/- each.

Through a new oral iron chelating drug known as L-1, CP20, DMPH, Deferiprone (Chemical Name, 1,2,Dimethyl 3 Hydroxypyridine 4-one) has been reported very recently, it is yet to establish its potentiality of patients suffering from the disease of Thalassemia. The reported side effects of this drug are 1. Myelotoxicity i.e. occurrence of neutropenia 2. Orthopathy i.e. skeleto-muscular pain and swelling around knee and hipjoints and lastly mild Zinc deficiency occasionally leading to dermatopathy (Reference may be made to the Proceedings of National Thalassemia Conference, 5-6 February, 1994, held in Delhi; L1: Oral Iron chelation Therapy-Indian Study by M.E. et al). The cost of a capsule Deferiprone is approximately 50 U.S. cents (Rs. 12/-). A patient has to take 3-6 capsules per day. This will amount to US \$ 70-90 (Rs. 1000-2000) per month.

Another method which is available for the treatment of the disease Thalassemia (major) is by the bone marrow transplantation (BMT). This is done by the taking the bone marrow of the matching donor and injecting it to the patient. The cost of such a treatment is around US \$ 50000/- (Rs. 15,00,000/-). This is therefore beyond the reach of common man. Several treatments using bone marrow have been performed in many parts of the world including U.S.A. and Italy. Recently, Christian Medical College (Vellore), India and Apollo Hospital (Madras) India have also started this type of BMT treatment in India, but the cost is also on the higher side (Rs. 7 Lac. approx). Further, increase in life span expectancy of these patients have yet to be established.

Under the prevailing present day conditions, regular blood transfusion and use of the drug 'Desferal' by injection as explained above, is the best way of treatment of this dreaded disease since a decade, efforts are being made by medical profession throughout the world to find a treatment of this disease by a drug which will be low cost and can be administered orally and have no side effects but there has been no success so far.

5 Therefore, the main objective of the present invention is to provide a formulation useful for iron-chelation for the treatment of Thalassemia.

Another objective of the present invention is to provide a formulation useful for the treatment of Thalassemia with increased therapeutic efficacy.

10 Yet another objective of the present invention is to provide a formulation for the treatment of Thalassemia which is much cheaper and hence affordable by a common man.

15 Still, another objective of the present invention is to provide a formulation useful for the treatment of patients suffering from Thalassemia which can be administered orally.

Further objective of the present invention is to provide a formulation which has no side effect and is very convenient to administer.

20 Another object of the present invention is to provide a formulation useful for the treatment of Thalassemia, the dose of which can be continued for a long period without damaging any vital organ of the body of the patients.

With the above objectives in view our work initially directed in red blood cells and at the same time, to enhance the oxygen carrying capacity to the tissues. Different compounds of Vanadium, Arsenic, oxalic acid and citric acid were tried initially but these compound failed in making a major breakthrough.

25 It has been observed that patients suffering from Thalassemic disease have a change in complexion, anorexia, blackness of gums, increase in serum ferritin level and a remarkable iron overload in the body due to the breaking down of red blood cells. The treatment mentioned above which involves repeated blood transfusion also accumulates the above elements in the body of the patients suffering from Thalassemic disease.

Children suffering from Thalassemia disease do not show any resistance from viral infection and also suffer from 30 body ache. They are also immune to malaria.

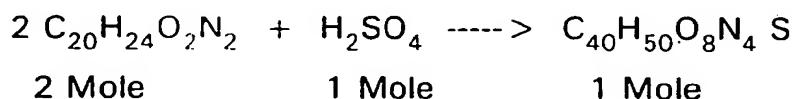
Our research work was primarily directed to find an immediate solution for the survival of such patients, who had an iron overload in the body and the other side ailments mentioned above.

Efforts, therefore, were directed towards finding out an alternate drug which can be used orally and have no side 35 effects. Anemonin Pretensis (powder) has been used for many years by tribals of Siberia to poison their arrows. Anemonin Pretensis is extracted with an organic solvent such as ethanol from fresh whole wind flower plant (the botanical name by Anemonin) with roots and flowers and some fruits of wind flowers. The dried material is treated with an organic solvent such as ethanol and refluxed. Anemonin Pretensis obtained from the extraction is filtered and recrystallized from an organic solvent such as ethanol. The medical history of this herb also reveals that this herb was involved in homeopathic practice in 1805 for some female hormone problem.

40 Anemonin Pretensis is a pure herbal product. This is present in the wind flower plant which is growing in wild state in the open fields and plains in many parts of Europe, Russia and Turkey in Asia. The chemical formula of Anemonin pretensis having the formula 1, shown in the drawing accompanying this specification, isolated from fresh wind flower plant is 1-2 dihydroxy 1-2 cyclobutane diacrylic acid di-lactone. Reference may be made to Merck index P-87, Entry no. 677, 9th edition.

45 Patients suffering from Thalassemic disease are immune to material attack. Considering the nature and considering that quinine sulphate a known antimalarial drug which has antipyretic and analgesic properties, we considered incorporating quinine sulphate in the formulation to reduce the high temperature and body-ache problem of the patients suffering from Thalassemic disease.

Quinine is having the chemical composition $C_{20}H_{24}N_2O_2$. It is obtained from Cinchona bark available in India, Sri 50 Lanka, Ecuador, Columbia, Peru and Bolivia. Cinchona thrives at higher elevation such as 6000-8500 ft. Quinine is also extracted with an organic solvent such as ethanol from the bark of the plant (Cinchone), refluxed, filtered and recrystallized with an organic solvent such as ethanol. Quinine sulphate is prepared by reacting quinine and dilute sulphuric acid in a (2:1) molar ratio as shown below.



Quinine Sulphate is a snow white, light odourless extremely bitter crystallized needles having the chemical composition $C_{40}H_{48}N_4O_4$, H_2SO_4 & H_2O . Reference may be made to Merck Index p-1049, entry no. 7879, 9th edition.

By our continuous and sustained research work based on the above mentioned directions, we observed that when

we blended (preferable mechanically) the powder of Anemonin Pretensis with quinine sulphate and dissolved in suitable solvent and the solution was administered orally to the patient suffering from Thalassemia, there was remarkable improvement of complexion and reduction of serum ferritin level. There was no fever. There was also no body ache. The treatment was continued and more patients were put on trial on this drug. There were no side effects. This revealed that the formulation is very useful in the treatment of the patients suffering from Thalassemia

Accordingly, the present invention provides a pharmaceutical formulation useful for treating patients suffering from thalassemia which comprises :-

- 10 i. Powder of Anemonin Pretensis in an amount in the range of 0.02 to 0.12 wt% of the formulation.
- ii. Quinine sulphate in an amount in the range of 0.0005 to 0.003 wt % of the formulation.
- 15 iii. Distilled or demineralised water in an amount in the range of 0 to 40 wt % of the formulation, and
- iv. Edible solvent 99.88 to 60 wt % of the formulation.

The solvent used may be selected from solvent ethanol ,absolute alchol etc.

The anemonin pretensis powder and the quinine sulphate employed in the formulation may be of pharmaceutical grade.

20 The Anemonin Pretensis possesses the properties of chelating iron. Quinine sulphate seems to accelearate the chelation of iron present in the body of the patient suffering from thalassemia. We have found by forming a formulation of Anemonin Pretensis and Quinine sulphate in the amount mentioned above results in an unexpected properties which are not present in the individual components. There is, therefore, a synergistic activity when they are combined in the above mentioned quantities.

25 The formulation of the present invention is therefore, not a mere admixture of the ingradients employed but a synergistic mixture, the properties of which are not merely the aggregate properties of the individual ingredients of the formulation.

The formulation of the present invention when administered to patients suffering from Thalssemic disease works as follows :-

30 The iron present in the body of the patients forms a complex with anemonin shown in formula 2 of the drawings (closed ring structure) or in formula 3 of the drawings (stretched structured) where three molecules of anemonin can form complex with two iron atoms. The quinine sulphate present in the formulation acts as a catalyst for the formation of the complex thereby not only reducing the amount of Anemonin in the complex/composition but also use the maximum amount of iron present in the body. In addition, the antipyretic and analgesic properties of quinine sulphate help to control the fever and the bodyache problem present in such patients.

35 The iron complex so formed in the body fluids. The fluid containing the complex reaches the kidney through the body system of the body and it is then excreted from the body of patients through urine. Some of the complex is also excreted through elemetary canal and finally facaeces. By this processes the excess iron present in the body of the patients is removed thereby enhancing the life span of the patients. The various ingredients of the present formulation can be blended by any conventional methods such as mechanically mixing etc.

40 The following examples are given by way of illustration and these should not be construed to limit the scope of the present invention.

Example 1

45 A formulation was prepared by blending the following ingredients :

Powder of Anemonin Pretensis	0.02 wt% of the formulation
Quinine Sulphate	0.0005 wt% of the formulation
Demineralised Water	10 wt% of the formulation
Ethanol Solvent	89.9795 wt % of the formulation

Example 2

A formulation was prepared by blending the following ingredients :

5	Powder of Anemonin Pretensis	0.04 wt% of the formulation
10	Quinine Sulphate	0.0008 wt % of the formulation
10	Demineralised Water	10 wt % of the formulation
10	Ethanol Solvent	89.9592 wt % of the formulation

Example 3

A formulation was prepared by blending the following ingredients :

20	Powder of Anemonin Pretensis	0.06 wt% of the formulation
25	Quinine Sulphate	0.001 wt % of the formulation
25	Demineralised Water	10 wt % of the formulation
25	Ethanol Solvent	89.939 wt % of the formulation

Example 4

A formulation was prepared by blending the following ingredients :

35	Powder of Anemonin Pretensis	0.08 wt% of the formulation
40	Quinine Sulphate	0.002 wt % of the formulation
40	Demineralised Water	10 wt % of the formulation
40	Ethanol Solvent	89.918 wt % of the formulation

Example 5

A formulation was prepared by blending the following ingredients :

50	Powder of Anemonin Pretensis	0.09 wt% of the formulation
55	Quinine Sulphate	0.001 wt % of the formulation
55	Demineralised Water	10 wt % of the formulation
55	Ethanol Solvent	89.919 wt % of the formulation

Example 6

A formulation was prepared by blending the following ingredients :

Powder of Anemonin Pretensis	0.12 wt% of the formulation
Quinine Sulphate	0.003 wt % of the formulation
Demineralised Water	10 wt % of the formulation
Ethanol Solvent	88.8779 wt % of the formulation

Example 7

A formulation was prepared by blending the following ingredients :

Powder of Anemonin Pretensis	0.09 wt% of the formulation
Quinine Sulphate	0.001 wt % of the formulation
Demineralised Water	80 wt % of the formulation
Ethanol Solvent	19.909 wt % of the formulation

25

Example 8

A formulation was prepared by blending the following ingredients :

30

Powder of Anemonin Pretensis	0.08 wt% of the formulation
Quinine Sulphate	0.001 wt % of the formulation
Demineralised Water	40 wt % of the formulation
Ethanol Solvent	59.919 wt % of the formulation

35

The formulations mentioned in Examples 1 to 8 were administered to patients of different age groups who were suffering from Thalassemia. The patients were administered the above formulation orally after mixing it with water. The formulation was administered to the patient daily. Such a treatment was continued for a period of two months. All the formulations showed that iron is excreted through urine after the administration of the formulation at a range from 10-95 %. This result points out that the formulation of the present invention is very effective for the chelation of iron, thereby reducing the serum ferritin level in the patients suffering from Thalassemia. Such a position results in longer and larger survival rate of the patients suffering from Thalassemia. The above mentioned results are shown in Table 1.

50

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Table-1

Effectivity of the formulation of the present invention.							
Formulation used	No. of patient treated	Age (yrs)	Sex	Frequency of transfusion (days)	Duration of treatment (months)	Medicine Administered in drops twice daily	Excretion chelated iron (%)
Example 1	3	5	M	22	2	15	15
		7	F				25
Example 2	3	7	F				25
		9	M	20	2	15	40
Example 3	3	9	M				25
		11	M				30
Example 4	3	7M		21	2	15	40
		7M					40
Example 5	3	9F					50
		15	M	20	2	15	70
Example 6	3	20	F				70
		23	F				80
Example 7	3	3	M	21	2	15	90
		9	F				91
Example 8	3	19	M				95
		10	M	22	2	15	20
Example 7	3	11	F				20
		12	M				30
Example 8	3	15	M	21	2	15	10
		16	F				15
Example 8	3	19	F				10
		7	M	20	2	15	75
Example 8	3	9	M				75
		11	F				80

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Table - 2

Comparison of Desferal, Defripron and the formulation of the present invention			
Name of the medicine	Mode of Administration	Side effects	Taste
Desferal	Injection (highly painful)	Adverse side effects such as :- a. ocular toxicity b. auditory meaurotoxicity c. cerebral toxicity d. allergic skin reaction e. cardiovascular and gastro-intestinal disturbances f. change in blood pressure	Does not apply
Defripron	Oral	More side effects than Desferal such as :- a. Myelotoxicity b. Arthropathy c. Mild Zine deficiency d. Questionable occurrence of immunological complications	Bitter taste
Formulation of the present invention	Oral	No side effects	Tasteless

Table - 3

Annual cost of treatment of Thalassemia using the hitherto known drugs and the formulation of the present invention.		
Name of medicine	Amount in US \$	Reference
DESFERAL	3000 - 6000	Iron Chelation Therapy C. Hershko & D.J. Weatherall CRC Critical Reviews Clinical Laboratory Series 26(4), 314, 1988
DEFRIPRONE (L-1)	800 - 1100	News Review, United Kingdom Thalassemia Soc Issue No. 61, March, 95
PRESENT FORMULATION	50 - 60	-----

Table 3 illustrates that the cost of the present formulation is the cheapest when compared with known drugs. The formulation of the present invention can be in the form of tablets, powder or suspension.

The main advantages of the formulation of the present invention are :-

1. Iron-chelation using the formulation of Anemonin Pretensis and Quinine sulphate is upto 90 %.
2. The cost of the formulation is around US \$ 5 to 10/- (Rs. 150-200/-) per 30 ml vial and it can be used for one month. The cost is much lower as compared to other currently available medicines in the market for the treatment of Thalassemia.

3. The formulation has no toxic effects even when it is administered for longer period.

4. The formulation is tasteless and odourless and can be administered orally.

5 **Claims**

1. A pharmaceutical formulation useful for treating patients suffering from thalassemia which comprises :-

- a. Powder of Anemonin Pretensis in an amount in the range of 0.02 to 0.12 wt % of the formulation,
- b. Quinine sulphate in an amount in the range of 0.0005 to 0.003 wt % of the formulation,
- c. Distilled or demineralised water in an amount in the range of 0 to 40 wt % of the formulation and
- d. Edible solvent 99.88 to 60 wt % of the formulation.

2. A pharmaceutical formulation as claimed in claim 1, wherein the edible solvent is present in an amount in the range of 99.88 to 59.889 wt %.

20 3. A pharmaceutical formulation as claimed in claim 1, wherein the Anemonin Pretensis is present in an amount selected from 0.04 wt %, 0.06 wt %, 0.08 wt % and 0.09 wt %.

4. A pharmaceutical formulation as claimed in claim 1, wherein the Anemonin Pretensis used is of pharmaceutical grade.

25 5. A pharmaceutical formulation as claimed in claim 1, wherein the solvent used is ethanol or absolute alcohol.

6. A pharmaceutical formulation as claimed in claim 1, wherein quinine sulphate used is of pharmaceutical grade.

30 7. A pharmaceutical formulation as claimed in claim 1, wherein the quinine sulphate is present in an amount selected from 0.0008 wt %, 0.001 wt %, and 0.002 wt %.

35 8. A pharmaceutical formulation as claimed in claim 1, wherein the solvent is present in an amount which is selected from 89.9795 wt %, 89.9592 wt %, 89.939 wt %, 89.918 wt %, 89.97 wt %, 89.95 wt %, 88.87 wt %, 89.92 wt %, 89.94 wt %, 19.909 wt % and 59.919 wt %.

9. A process for the preparation of a pharmaceutical composition for treating patients suffering from Thalassemia, said process comprising mixing :-

40 a. Powder of Anemonin Pretensis in an amount in the range of 0.02 to 0.12 wt % of the formulation,

b. Quinine sulphate in an amount in the range of 0.0005 to 0.003 wt % of the formulation,

c. Distilled or demineralised water in an amount in the range of 0 to 40 wt % of the formulation, and

45 d. Edible solvent 99.8 to 60 wt % of the formulation.

10. A process as claimed in claim 9, wherein the anemonin pretensis powder and the quinine sulphate used are of pharmaceutical grade.

50 11. A process as claimed in claim 9, wherein the solvent used is ethanol or absolute alcohol.

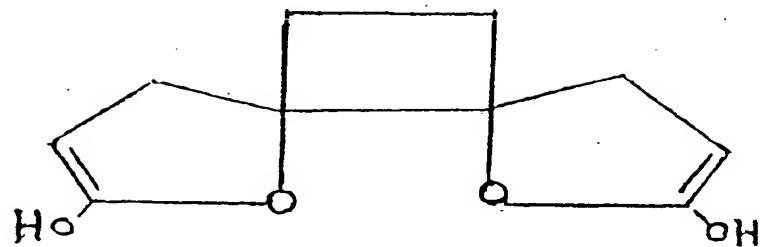


FIGURE - 1

STRUCTURE OF IRON - ANEMONIN COMPLEX

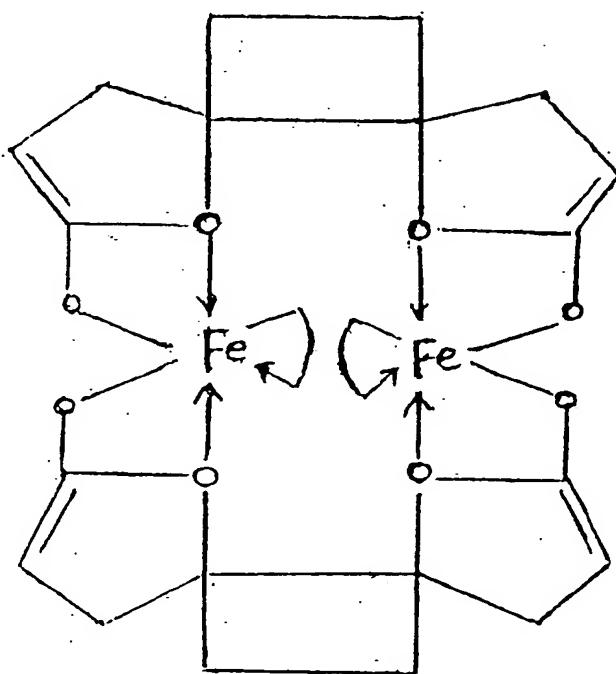


FIGURE - 2

STRUCTURE OF IRON - ANEMONIN COMPLEX

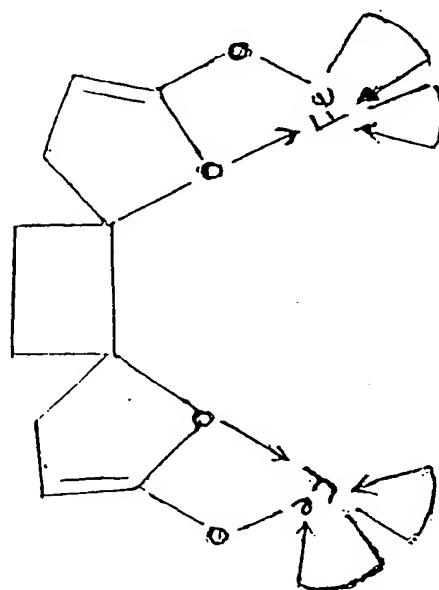


FIGURE - 3



EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.)						
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim							
A	GARNIER G.; BEZANGER-BEAUQUESNE L.; DEBRAUX G. 'RESSOURCES MEDICINALES DE LA FLORE FRANCAISE' 1961, PARIS, VIGOT FRERES; FR * page 425 - page 427 *	1-11	A61K31/49 //(A61K31/49, 31:365)						
A	HEINZ A. HOPPE 'DROGENKUNDE' 1958, GRAM, DE GRUYTER & CO, HAMBURG * page 73-74 *	1-11							
			TECHNICAL FIELDS SEARCHED (Int.Cl.)						
			A61K						
<p>The present search report has been drawn up for all classes.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of search</td> <td style="width: 34%;">Name of examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>11 January 1996</td> <td>Leenhouts, C.</td> </tr> </table>				Place of search	Date of completion of search	Name of examiner	THE HAGUE	11 January 1996	Leenhouts, C.
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THE HAGUE	11 January 1996	Leenhouts, C.							
<p>CATEGORY OF CITED DOCUMENTS</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top;"> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document </td> <td style="width: 50%; vertical-align: top;"> T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document </td> </tr> </table>				X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document	T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document				
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document	T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document								



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which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application number
EP 88 73 0052

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
	No search has been performed	1-44	A 61 K 41/00 A 61 K 43/00 A 61 K 33/26 A 61 K 9/50
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely:</p> <p>Claims searched incompletely:</p> <p>Claims not searched: 1-44</p> <p>Reason for the limitation of the search:</p> <p>Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)</p>			
Place of search The Hague	Date of completion of the search 07-11-1988	Examiner BRINKMANN	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			